

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 11 JUL 2006

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Applicant's or agent's file reference 15186-46PCT		<b>FOR FURTHER ACTION</b>		See Form PCT/PEA/416
International application No. PCT/IB2004/003559		International filing date (day/month/year) 29.10.2004		Priority date (day/month/year) 31.10.2003
International Patent Classification (IPC) or national classification and IPC G01N21/64, A61B5/00				
Applicant ART ADVANCED RESEARCH TECHNOLOGIES INC. et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand  30.08.2005		Date of completion of this report  27.09.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized Officer  D'Alessandro, D  Telephone No. +31 70 340-		



**INTERNATIONAL PRELIMINARY REPORT  
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International application No.  
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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-21 as originally filed

**Claims, Numbers**

1-42 as originally filed

**Drawings, Sheets**

1/6-6/6 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
  - ☒ claims Nos. 9,18  
because:
    - ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
    - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
    - ☒ the claims, or said claims Nos. 9,18 are so inadequately supported by the description that no meaningful opinion could be formed.
    - ☐ no international search report has been established for the said claims Nos.
    - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
      - the written form ☐ has not been furnished
      - ☐ does not comply with the standard
      - the computer readable form ☐ has not been furnished
      - ☐ does not comply with the standard
    - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
  - ☒ See separate sheet for further details

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	1-8,10-17,19-42
	No: Claims	1-6,9-17
Inventive step (IS)	Yes: Claims	
	No: Claims	1-8,10-17,19-42
Industrial applicability (IA)	Yes: Claims	1-8,10-17,19-42
	No: Claims	

**2. Citations and explanations (Rule 70.7):**

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

With reference to the feature of claims 9, 18:

obtaining the scatter coefficient and the lifetime of the fluorophore using time-domain optical measurement of the medium;

there is no teaching in the application description (see page 11, l. 11-13), about how the skilled person could carry out the claimed method, starting from the embodiment disclosed in the application. These claims therefore lack support (Art. 6 PCT), and no opinion on novelty and inventive step was given.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1: US-B1-6 321 111 (PERELMAN LEV T ET AL) 20 November 2001 (2001-11-20)  
D2: US-A-4 135 816 (NIEMANN ET AL) 23 January 1979 (1979-01-23)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-8,10-17,19-42 does not involve an inventive step in the sense of Article 33(3) PCT.

1. The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses (the references applying to this document):

*col. 2, l. 19-28*

A method determining depth of a volume comprising a fluorophore in a turbid medium using time domain (TD) optical fluorescence,

- |                          |   |
|--------------------------|---|
| <i>col. 6, l. 49-52;</i> | i) obtaining at least one temporal point spread function          |
| <i>col. 6, l. 61 -</i>   | (TPSF) by injecting light at an injection point at an             |
| <i>col. 7, l. 6;</i>     | excitation wavelength of said fluorophore and detecting           |
| <i>figs. 6A, 6B</i>      | light at a detection point at an emission wavelength of           |
|                          | said fluorophore;   |
| <br>                     |   |
| <i>col. 7, l. 8-23;</i>  | ii) determining a time $t_{1/2}$ , at which the TPSF signal       |
| <i>fig. 7</i>            | reaches half-maximum;   |
|                          | iii) correlating said $t_{1/2}$ with said depth, to determine the |
|                          | depth, wherein said depth is insensitive to fluorophore           |
|                          | concentration.  |

The subject-matter of claim 1 differs from these disclosures of D1, in that the time instant correlated with the fluorophore depth is the time  $t_{\max}$  corresponding to the maximum of the fluorescence curve and not the rise-time  $t_{1/2}$  of D1.

However, the dependence of  $t_{\max}$  from the fluorophore depth, in certain conditions, is shown in document D1 (fig. 6A). Therefore, said time instant merely represents a known alternative to the use of  $t_{1/2}$  of D1, that the person skilled in the art would choose without an inventive effort depending on the circumstances. For these reason, the subject-matter of claim 1 does not involve an inventive step (Art. 33(3) PCT).

2. Dependent claims 2-27 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step. These claims actually refer to design options that are common in the art (see also documents D1, D2 and the passages cited in the search report).

In the following paragraphs, brief additional reasons are given regarding the main features of these claims.

2.1 The generation of a tomographic image (claims 24, 25) is disclosed by document D1 (*col. 9, l. 17-24*).

2.2 The measurement of the fluorophore concentration by detecting the fluorophore emission intensity (claims 13-23) is well-known in the art (see for example document D2, *col. 8, l. 56-64*).

2.3 The correlation of fluorophore depth and fluorescence intensity (claim 26), for the measurement of the fluorophore concentration, is obvious for the person skilled in the art. It is actually well-known that the intensity depends on the concentration and on the depth of the fluorophore (see also document D1 *col.7, l. 47-49*).

2.4 The speed of light (depending on the refractive index) and the scattering coefficient of the medium, as in claims 5,10-12,17,19-21, are parameters that the person skilled in the art would take into account when performing these measurements (see D1, *col. 37-59; col. 13, l. 39-47; eq. 6; fig. 12*).

3. Document D1 discloses also the following features of the apparatus of independent claim 28:

<i>Fig. 1A;</i> <i>col. 4, l. 42-56</i>	An apparatus [suitable] for determining the depth and the concentration of a fluorophore in a turbid medium, comprising: a light source (10), optically coupled to a source channel (14) and said object (16), to inject light in said object at a desired point and excitation wavelength; a detector channel (18), optically coupled to a photon detector (22) and said object,
<i>col. 4, l. 56-62</i>	in a backreflection geometry relative to said source channel,
<i>col. 5, l. 21-24</i>	to acquire at least one temporal point spread function from a desired point to determine depth of said fluorophore;
<i>col. 5, l. 16-20;</i> <i>col. 7, l. 8-13</i>	a depth calculator (24).

The feature: "means for spatially positioning the object relative to the channel" is clearly included in the apparatus of D1.

The subject-matter of claim 28 also includes the features:

A) a second detector channel in a trans-illumination geometry relative to the source

channel, to measure an emission intensity of said fluorophore;  
B) a concentration calculator;

The technical problem addressed by these features is the measurement of the fluorophore concentration by detecting the intensity of the fluorescence radiation emitted by the object. Document D2 discloses an apparatus for measuring the concentration of a chemical in a sample (*col. 5, l. 5-11; col. 8, l. 56-62*), by means of fluorescence detection in a trans-illumination geometry (see in figs. 1,3 the arrangement of lamp **5**, mirror **12**, sample vessel **11**, emission filter **24** and detector **16**). Features A and B are therefore disclosed by D2, solving the same technical problem as in the present application.

The person skilled in the art knows that, in the apparatuses like in D1, several detection channels may be added, according to the circumstances. Therefore, to solve the technical problem stated above, the skilled person would not need an inventive effort to implement in the apparatus of D1 a trans-illumination channel, as disclosed by D2, therefore reaching the subject-matter of claim 28. The subject-matter of claim 28 does not therefore involve an inventive step (Art. 33(3) PCT).

3.1 Dependent claims 29-42 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, because they represent common design options in the field.